Euthyroid Hyperthyroxinemia and Euthyroid Hypothyroxinemia — Differential Diagnosis and T3-Resin Uptake

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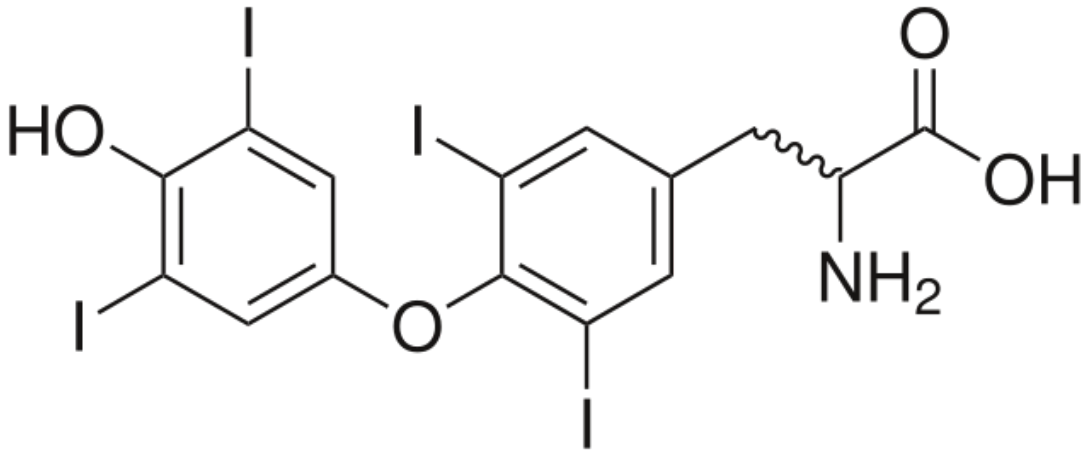
The thyroid gland is an endocrine organ that secretes the hormones triiodothyronine (T3) and thyroxine (T4), which are, in turn, under the influence of the TSH and the TRH. Though hyper- and hypothyroidism remain the common clinically manifesting condition of the thyroid, in some cases, the patient remains symptomless with either excess or decrease in thyroxine levels, along with normal TSH levels. This is termed as euthyroid hyperthyroxinemia and euthyroid hypothyroxinemia, respectively. The cause is altogether different from the thyroid and should not be inappropriately managed as hyperthyroid and hypothyroid states.



Thyroid Hormones

Of the two thyroid hormones, **thyroxine (T4)** is the primary hormone secreted by the thyroid gland with **triiodothyronine (T3)** being secreted in lesser amounts. T3, however, has much greater biological activity compared to T4 and is generated at its site of action peripherally by **deiodination** of T4.

Biochemical characteristics

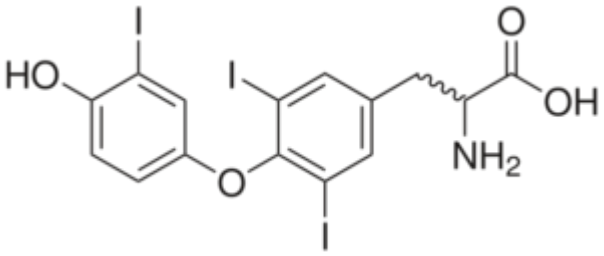


Image: “2D structure of thyroid hormone triiodothyronine.” by Harbin – Own work. License: Public Domain

The normal total serum T4 levels are approximately 103 nmol/L, and the total serum T3 levels are approximately 2.3 nmol/L.
T4 and T3 are relatively lipophilic; thus, their free forms in the plasma are in equilibrium with the much larger pool of protein-bound thyroid hormones in the plasma and within tissues.

Free thyroid hormones are added to the circulating pool by the thyroid gland. It is the free thyroid hormones that are physiologically active, and that is implicated in the feedback to inhibit pituitary secretion of TSH. The function of protein-binding appears to be the maintenance of a large pool of hormones that can readily be mobilized as needed.

Features of the bound protein

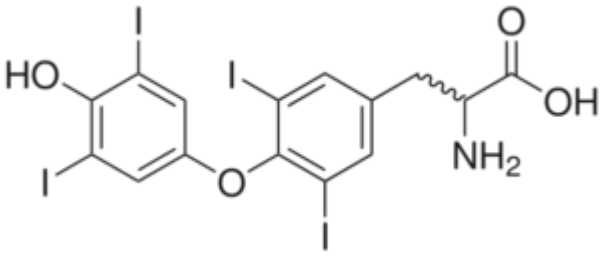


Image: “2D structure of the thyroid hormone thyroxine.” by Harbin – Own work. License: Public Domain

The plasma proteins that bind thyroid hormones are **albumin**, prealbumin, known as **transthyretin** (formerly known as thyroxine-binding prealbumin) and a globulin known as **thyroxine-binding globulin (TBG)**. The affinities of the thyroid hormone-binding proteins are such that most of the circulating T4 is bound to TBG, with lesser amounts being bound to transthyretin and albumin.

Normally, 99.98 % of the total serum T4 is bound to proteins, with very little excretion of T4 in the urine. 99.8 % of T3 is bound. TBG binds approximately 75 % of the circulating T4 and T3, because of its high affinity. Thyroxine-binding prealbumin binds to only about 15 % of the hormones, and albumin binds to the remaining 10 %. Despite having the largest binding capacity, the thyroid hormones bind least avidly to albumin.

Outcomes of an alteration in the thyroid binding proteins

When a sudden, sustained increase in the concentration of thyroid-binding proteins in the plasma takes place, the concentration of the free thyroid hormones falls. This change is only transient.

However, the decrease in the levels of free thyroid hormones in the serum stimulates **TSH secretion.** This, in turn, normalizes thyroid hormone levels by stimulating an

increase in the production of free thyroid hormones. Therefore, patients with increased or decreased levels of thyroid hormone-binding proteins, particularly TBG, are typically neither **hyperthyroid** nor hypothyroid but, rather **euthyroid**.

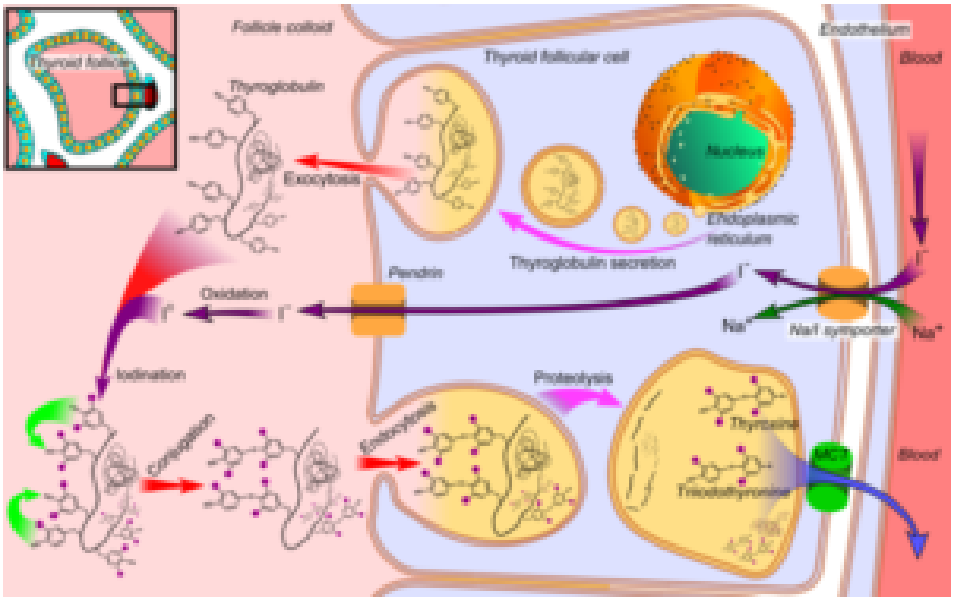


Image: "Thyroid hormone synthesis" by Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine. License: CC0

Causes for the change in the thyroid binding protein level

Changes in the plasma concentrations of the thyroid hormones' binding proteins mentioned above, particularly TBG because of its high affinity, can lead to **changes in the total plasma T4 and T3 levels**.

Variations in the concentration of TBG can either be congenital or acquired. TBG levels can be raised in the following settings: pregnancy, estrogen-treated patients, and some drugs. TBG levels can be lowered by excesses of hormones such as **glucocorticoids** or **androgens**, some drugs such as **dazanol** and **L-asparaginase** (a cancer chemotherapeutic agent).

Other drugs such as **salicylates**, **phenytoin** (an anticonvulsant), **mitotane** and **5-fluorouracil** (cancer chemotherapeutic agent) inhibit the binding of the thyroid hormones to TBG and consequently produce changes similar to those produced by a decrease in the concentration of TBG.

Euthyroid Hyperthyroxinemia

Definition of euthyroid hyperthyroxinemia

Euthyroid hyperthyroxinemia is defined as a condition in which there is an increase in the serum total thyroxine and triiodothyronine levels, with concomitant normal thyroid-stimulating hormone serum levels and no signs and symptoms of thyroid pathology.

Etiology of euthyroid hyperthyroxinemia

Euthyroid hyperthyroxinemia follows abnormalities of the binding proteins and is usually a result of an increase in the binding proteins. As much as any of the binding proteins can be affected, TBG is usually the one commonly affected, with TBG excess being the commonest binding-protein abnormality.

Some of the causes of euthyroid hyperthyroxinemia include:

Hereditary: Familial **dysalbuminemic hyperthyroxinemia** is a hereditary condition that usually results from mutations in TBG, TTR or albumin, leading to an increase in their binding affinity for T4 and/or T3. The affected patients, therefore, have increased serum total T4 levels but are euthyroid (unbound hormone levels are normal) with normal serum TSH levels.

Estrogen: Estrogen increases serum TBG levels by slowing down its clearance. This is accomplished by causing glycosylation of TBG, which in turn reduces the rate of clearance of TBG, resulting in increased serum concentration. Therefore, serum TBG levels are usually increased in pregnant women, women using oral contraceptives, women on postmenopausal estrogen therapy and patients with estrogen-secreting tumors.

Hepatitis: acute and sub-acute hepatitis cause a rise in the serum levels of TBG.

Drugs: a number of drugs cause a rise in the serum levels of TBG. These drugs include methadone and tamoxifen.

Acute intermittent porphyria: serum TBG levels may be raised in acute intermittent porphyria.

Reduced thyroxine deiodination: as mentioned earlier, thyroxine is usually deiodinated peripherally to form triiodothyronine. Some drugs, however, inhibit this process resulting in hyperthyroxinemia with normal serum thyroid-stimulating hormone (TSH) levels. These drugs include amiodarone, propranolol and iodinated contrast agents such as ipodate and iopanoic acid.

Euthyroid Hypothyroxinemia

Definition of euthyroid hypothyroxinemia

Euthyroid hypothyroxinemia is defined as a condition in which there is a decrease in the serum total thyroxine and triiodothyronine levels, with concomitant normal thyroid-stimulating hormone serum levels and no signs and symptoms of thyroid pathology.

Etiology of euthyroid hypothyroxinemia

Euthyroid hypothyroxinemia also follows abnormalities of the binding proteins and is usually as a result of a decrease in the binding proteins.

Some of the causes of euthyroid hyperthyroxinemia include:

Displacement of T4 from binding proteins

Some drugs displace T4 from their binding proteins resulting in reduced total T4 levels, but with normal serum free T4 levels. These drugs occupy the binding sites that would

normally be bound by T4, therefore, causing a fall in the total T4 levels. Examples of such drugs include salicylates, high-dose furosemide in chronic kidney disease patients, NSAIDs, Mefenamic acid.

Hereditary

Hereditary TBG deficiency is an X-linked disorder characterized by very low levels of total T4 and T3. However, because unbound hormone levels are normal, patients are euthyroid and TSH levels are normal. It is important to recognize this disorder to avoid inappropriate efforts in trying to normalize total T4 levels, as it may lead to thyrotoxicosis and is usually futile due to the rapid clearance of the unbound thyroid hormone in the absence of TBG.

Hormonal excess

Hormonal excess such as androgens in high doses, glucocorticoids, or the hormonal excesses observed in acromegaly and Cushing's syndrome, may cause a fall in the serum TBG levels resulting in reduced total serum T4 levels.

Nephrotic syndrome

Nephrotic syndrome, which is characterized by urinary loss of proteins, causes urinary loss of TBG, which in turn can result in hypothyroxinemia. Usually, the patients are euthyroid, hence euthyroid hypothyroxinemia, but hypothyroidism may occur in some patients.

Medication

Some drugs lower serum TBG levels, presumably by decreasing production of TBG. These drugs include L-asparaginase, danazol, niacin.

Laboratory Investigations

A **thyroid profile** measures serum TSH, thyroxine and triiodothyronine levels. Total T4 and T3 can both be measured by **radioimmunoassay**.

There are also direct assays that specifically measure only the free forms of these hormones. The latter is more clinically relevant measures, given that these are the active forms, and also due to both acquired and congenital variations in the concentrations of binding proteins between individuals.

Depending on these thyroid hormone levels and clinical presentation, different diagnoses can be made. **The following table summarizes the same:**

Diagnosis	TSH	Free T4	Signs and symptoms
Primary hyperthyroidism	Decreased	Increased	Hyperthyroidism
Secondary hyperthyroidism; TSH secreting tumor	Increased	Increased	Hyperthyroidism
Primary hypothyroidism	Increased	Decreased	Hypothyroidism
Secondary hypothyroidism; Hypopituitarism	Decreased	Decreased	Hypothyroidism
Subclinical hyperthyroidism	Decreased	Normal	None
Subclinical hypothyroidism	Increased	Normal	None
Euthyroid hyperthyroxinemia	Normal	Increased	None
Euthyroid hypothyroxinemia	Normal	Decreased	None

Special Test – Aiding in the Distinguishing

Triiodothyronine (T3)-resin uptake test

The triiodothyronine (T3)-resin uptake test was designed in part to **detect abnormalities in serum TBG** which would in turn aid in diagnosing euthyroid hyperthyroxinemia and hypothyroxinemia. These, as mentioned above, are usually a result of abnormalities of the thyroid hormones' binding proteins.

The test measures the **number of unoccupied T4-binding sites** and is performed by incubating the patient's serum with **radio-labeled T3**. **Resin** is added afterward. The radio-labeled T3 will bind the serum proteins (such as TBG), and any excess radio-labeled T3 will bind the resin that has been added subsequently.

Interpretation of the triiodothyronine (T3)-resin uptake test

In body states where there is an excess of TBG, more radio-labeled T3 will bind TBG and less will bind the resin, resulting in low T3-resin uptake. As expected, these results are reversed in body states with reduced TBG. In TBG deficiency, less radio-labeled T3 will bind TBG causing more of it to bind resin, and hence there is a high T3-resin uptake.

Expected outcome in the triiodothyronine (T3)-resin uptake test

The expected changes in serum-free T4 index, serum total T4, and T3-resin uptake in hyperthyroidism, hypothyroidism, TBG excess, and TBG deficiency can be summarized as follows:

Diagnosis	Serum Free T4 Index	Serum Total T4	T3-Resin uptake/ THBR
Hyperthyroidism	Increased	Increased	Increased
Hypothyroidism	Decreased	Decrease	Decreased
TBG excess	Normal	Increased	Decreased
TBG deficiency	Normal	Decreased	increased

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